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09/872,712	06/01/2001	Marina V. Backer	102131-200	4250

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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	8

DATE MAILED: 07/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/872,712	Applicant(s) BACKER ET AL.	
	Examiner Richard Schnizer	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *10,24 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-23,25-39 and 41-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

An amendment was received and entered as Paper No. 7 on 5/7/02. Claims 46-57 were canceled as requested. Applicant's election with traverse of group I and the species of copolymer, nucleic acids, wild type S-protein fragment of bovine RNase A, growth factors, and water is acknowledged. No grounds for traversal were given. The requirement is still deemed proper and is therefore made FINAL.

It is noted that Applicant has characterized the election of each species in terms of claims in which species were recited, e.g. at page 3 of the response: "Applicants herein elect with traverse the species of co-polymers recited in claim 6." This language has been interpreted to mean that this election applies to all claims on which the elected species are readable, and not just to the recited claim. The combination of species elected is readable on claims 1-9, 11-23, 25-39, and 41-45. Claims 10, 24, and 40, withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7. Claims 1-45 are pending and claims 1-9, 11-23, 25-39, and 41-45 are under consideration in this Office Action.

A search of the prior revealed that claims directed to the elected combination of species, i.e. co-polymer, nucleic acids, wild type S-protein fragment of bovine RNase A, growth factors, and water, were free of the art. In accordance with MPEP 803.02, the Office has extended the

search to a second combination of species, *i.e.* liposomes, nucleic acids, streptavidin, antibodies, and water. Claims reciting these species have been found to be anticipated and obvious over the prior art for the reasons given below under 35 USC 102 and 103 rejections. However, claims 12, 26, and 42 were free of the art when considered in terms of any combination of the species set forth in the species election requirement, so these claims have been considered in terms of their broad generic claims, and have been found to be anticipated as discussed below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 18, and 34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 4, 18, and 34 lack enablement because the invention as claimed is in inoperable. The claims require a composition comprising a carrier for carrying compounds, an adapter covalently linked to the carrier, and a targeting protein with a recognition portion and a targeting portion, wherein the recognition portion can bind to the adapter, and the targeting portion can bind to the target. These claims also require that the adapter must function as the target. The

specification fails to teach how to use this arrangement to carry any compound to the target, i.e. to the adapter protein, or why one would wish to do so. The only use asserted by the specification for using the adapter as a target is in coating artificial surfaces with a protein. See e.g. page 10, lines 27-30. In this context, the artificial surface would be analogous to the carrier, and the targeting protein appears to be analogous to the carried compound. This embodiment does not correspond to the claimed invention because it does not employ a carrier that functions to carry a compound to the target, i.e. the carrier does not carry the targeting protein to the adapter.

Because the specification fails to teach how to use the claimed invention as intended, and it is not readily apparent how it could be used, one of skill in the art would have to perform undue experimentation in order to discover how to use the invention.

Even if Applicant is able to overcome this ground of rejection, the following scope of enablement rejection would still apply.

Claims 1-9, 11-23, 25-39, and 41-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions and methods for delivery of nucleic acid diagnostic compounds and nucleic acid research compounds to a target, does not reasonably provide enablement for compositions and methods for delivery of therapeutic nucleic acids to a target. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The elected invention embraces methods and compositions for delivering therapeutic diagnostic or research compounds to a target, wherein the compound is a nucleic acid. The specification does not limit the types of therapy or diagnosis for which the nucleic acid may be used, thus the elected invention is considered to be very broad, encompassing diagnosis and therapy of any disease or disorder.

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by two recently published reviews. Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30).

While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller et al. reviews the types of vectors available for *in vivo* gene therapy, including retroviral, adenoviral, liposomal, and molecular conjugates, and conclude that "for the long-term success as well as the widespread applicability

of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain reviews ligand-targeted receptor mediated vectors, and indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise, but which are currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each. Verma clearly indicates that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see entire article). Verma discusses the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239 and 2nd and 3rd column of page 242. Verma also indicates that appropriate enhancer-promoter sequences can improve expression, but that the "search for such [useful] combinations is a case of trial and error for a given cell type" (page 240, sentence bridging columns 2 and 3). Crystal also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). While applicants specification supports efficient transfer for *ex vivo* and *in vivo* direct injection

into the organ, the specification fails to teach one of skill in the art how to overcome the unpredictability for vector targeting such that efficient gene transfer is achieved by any mode of delivery. The specification fails to teach any specific targeting techniques, fails to provide any working examples which encompass vector targeting, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art which would allow one of skill in the art to practice the claimed invention without undue experimentation.

More recently, Romano et al (2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. This idea was echoed by Somia and Verma (2000), shortly after the filing of the instant application, who noted that delivery vehicles still represented the Achilles heel of gene therapy, and that no single vector existed that had all of the attributes of an ideal gene therapy vector. See page 91, column 1, lines 5-13 of first paragraph. It should be noted that these authors considered viral vector designs similar to those of the instant invention in which adapter molecules are used to alter viral tropism. See page 97, column 1, lines 7-19.

Against this background, the specification provides no working examples or of gene therapy or guidance as to how to overcome the art-recognized problems of delivery and expression. No novel targeting ligands or targets are disclosed. Rather the emphasis of the

invention is on facilitating the use of existing targeting molecules. There is no evidence or reasoning to suggest that the compositions or methods of the instant invention will solve any of the art recognized barriers to general gene therapy.

In view of the state of the art of therapeutic nucleic acid delivery and expression, the absence of guidance or working examples regarding therapeutic nucleic acid delivery and expression, and the breadth of therapeutic applications embraced by the claims, one of skill in the art could not use the claimed methods and compositions commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12 26, 31-39, and 41-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12, 26, and 42 are indefinite because they recite "the N-terminus of said targeting protein" without antecedent basis. One of ordinary skill in the art appreciates that antibodies, one of the contemplated species of targeting proteins, comprise at four N-termini associated with the ends of each of the four polypeptide chains in an antibody. Furthermore, all proteins containing lysine residues contain one N-terminus corresponding to each lysine. Thus one of skill in the art cannot know to which N-terminus the claim refers.

Claims 31-39, and 41-45 are indefinite because the method steps are not concordant with the purpose set forth in the preamble. The claimed methods require delivery of a compound to a target, but the claims recite no step at which this takes place. The claims recite "administering" a composition, but it is not clear to what the composition is administered.

Claim 33 is indefinite because it is ungrammatical. The phrase "target is a" is recited twice consecutively.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5-9, 13-17, 19-23, 27-29, 31-33, 35-39, and 43-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Bally et al (US Patent 4,885, 172, issued 12/5/1989).

Bally teaches a composition and methods for delivering bioactive materials comprising a liposomal carrier, wherein the lipids are covalently modified with the adapter streptavidin, and biotinylated targeting antibodies are then bound to the adapter. See abstract. The bioactive material may be a polynucleotide. See column 6, lines 24 and 25. The antibodies may recognize cell surface antigens. See e.g. column 4, lines 15-17. Claims 5, 19, and 35 are included in the

rejection because the lipids comprise polymers of methylene groups in their hydrophobic tails, and because the carried nucleic acid can also be considered to be a polymer comprised by the carrier. Claims 13, 27, and 43 are included in this rejection because Bally teaches the use of antibodies to target liposomes to the class I MHC antigen, H-2. See column 2, lines 15-18. Class I MHC molecules such as H-2 are present on all nucleated cells including vascular endothelial cells.

Thus Bally anticipates the claims.

Claims 1-3, 5-7, 9, 12-17, 19-21, 23, 26-29, 31-33, 35-37, 39, 42, 44, and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Tillman et al (J. Immunol. 162(11): 6378-6383, 1999).

Tilmann teaches methods and composition for redirecting the tropism of adenoviruses carrying diagnostic nucleic acid encoding luceiferase. See abstract. A bispecific antibody which recognizes both the adenovirus fiber protein knob domain and the cell surface target CD-40 is used as a targeting protein. See entire document, especially abstract, and lines 5-10 of paragraph bridging pages 6379 and 6380. In the terminology of the instant invention, the knob domain can be considered to be an adapter which is covalently bound to the fiber protein and adenovirus carrier, the bispecific antibody is considered to be a targeting protein comprising a recognition domain (the portion of the antibody that recognizes the knob domain), and a targeting portion (the portion of the antibody that recognizes CD-40). Claims 12, 26, and 42 are included in this

rejection becasue one of ordinary skill in the art appreciates that the antigen binding domains of antibodies are comprised of N-terminal domains of the light and heavy chains. Claims 13, 27, and 43 are included in this rejection because CD-40 is expressed on a wide variety of cells, including vascular epithelial cells.

Thus Tillman anticipates the claims.

Claims 1-3, 6, 7, 9, 12, 14-17, 19-21, 23, 26, 28, 29, 31-33, 35-37, 39, 42, 44, and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Wickham et al (US Patent 5,712, 136, issued 1/27/98).

Wickham discloses methods and composition for redirecting the tropism of adenoviruses. See column 3, line 59 to column 4, line 3. This passage discloses a composition comprising an adenovirus with a modified fiber protein, and a bispecific antibody which recognizes a modified fiber protein and a target antigen. In the terminology of the instant invention, the portion of the fiber protein to which the antibody binds can be considered to be an adapter which is covalently bound to the adenovirus carrier, the bispecific antibody is considered to be a targeting protein comprising a recognition domain (the portion of the antibody that recognizes the fiber protein), and a targeting portion (the portion of the antibody that recognizes the target). One of ordinary skill in the art appreciates that the antigen binding domains of antibodies are comprised of N-terminal domains of the light and heavy chains.

Thus Wickham anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Bally et al (US Patent 4,885, 172, issued 12/5/1989), Tillman et al (J. Immunol. 162(11): 6378-6383, 1999), or Wickham et al (US Patent 5,712, 136, issued 1/27/98)..

Bally teaches a composition for delivering bioactive materials comprising a liposomal carrier, wherein the lipids are covalently modified with the adapter streptavidin, and biotinylated targeting antibodies are then bound to the adapter. See abstract. The bioactive material may be a polynucleotide. See column 6, lines 24 and 25. The antibodies may recognize cell surface antigens. See e.g. column 4, lines 15-17. Claims 5, 19, and 35 are included in the rejection because the lipids comprise polymers of methylene groups in their hydrophobic tails, and because the carried nucleic acid can also be considered to be a polymer comprised by the carrier. Claims 13, 27, and 43 are included in this rejection because Bally teaches the use of antibodies to target liposomes to the class I MHC antigen, H-2. See column 2, lines 15-18. Class I MHC molecules such as H-2 are present on all nucleated cells including vascular endothelial cells.

Tilmann teaches methods and composition for redirecting the tropism of adenoviruses carrying diagnostic nucleic acid encoding luceiferase. See abstract. A bispecific antibody which recognizes both the adenovirus fiber protein knob domain and the cell surface target CD-40 is used as a targeting protein. In the terminology of the instant invention, the knob domain can be considered to be an adapter which is covalently bound to the fiber protein and adenovirus carrier, the bispecific antibody is considered to be a targeting protein comprising a recognition domain (the portion of the antibody that recognizes the knob domain), and a targeting portion (the portion of the antibody that recognizes CD-40).

Wickham discloses methods and composition for redirecting the tropism of adenoviruses. See column 3, line 59 to column 4, line 3. This passage discloses a composition comprising an adenovirus with a modified fiber protein, and a bispecific antibody which recognizes a modified fiber protein and a target antigen. In the terminology of the instant invention, the portion of the fiber protein to which the antibody binds can be considered to be an adapter which is covalently bound to the adenovirus carrier, the bispecific antibody is considered to be a targeting protein comprising a recognition domain (the portion of the antibody that recognizes the fiber protein), and a targeting portion (the portion of the antibody that recognizes the target).

It is noted these references do not explicitly teach the organization of the elements of the composition into a kit with instructions for use. However, it would have been obvious to organize these materials into a kit with instructions for use because one of skill in the art

appreciates that organizing experimental reagents prior to use and following established protocols is standard laboratory practice which reduces the frequency of errors.

Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed. Claims 4, 11, 18, 25, 34, and 41 are free of the art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JAMES KETTER
PRIMARY EXAMINER